PATENT
Attorney Docket No. HILLS1100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Foster et al.	Art Unit:	1618
Application No.:	10/017,135	Examiner:	H.N. Sheikh
Filed:	December 7, 2001	Conf. No.	8942
Title:	SYNTHESIS OF SMALL PARTICLES		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Linda Sze Tu, hereby declare and state as follows:

1. My present position is Head of Operations of Eiffel Technologies Limited. Eiffel Technologies Limited is a licensee of the assignees of this patent application, The University of Sydney and Unisearch Ltd. I am authorized to make this declaration on behalf of the assignees.

2. I hold a Ph.D. in chemical engineering and have previously worked as a research and development engineer. My Ph.D. thesis was entitled 'The precipitation of fine pharmaceuticals using dense gas antisolvent' and I have worked at Eiffel Technologies Limited on developing various dense gas antisolvent processes since 2003. My current *curriculum vitae* and publications list is submitted herewith as Annexure LST1.

3. I have read U.S. Patent Application Serial No. 10/017,135 and am familiar with the prosecution history thereof.

4. I understand the Examiner has maintained the rejection of claims 1-20 and 28 under 35 U.S.C. §103(a) as allegedly being obvious over Debendetti et al. (U.S. Patent No. 6,063,910) in view of Merrified et al. (WO 00/37169) in the Office Action mailed January 11, 2008.

5. Additionally, I understand claims 30-35 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Debendetti et al. (U.S. Patent No. 6,063,910) in view of Merrified et al. (WO 00/37169).

6. I understand the Examiner alleges that my previous declaration submitted under 37 C.F.R. §1.132 with the Response to the Office Action filed October 25, 2007, is insufficient to overcome the rejection of claims 1-20. In dismissing the declaration, it appears the Examiner has taken issue with some of my conclusions regarding the teachings of references cited in the declaration.

7. In my opinion, determining whether to apply a linear or non-linear model to a given supercritical system, is by no means routine and requires significant effort. This is in part due to the complexity and unpredictable nature of supercritical systems that results from the high propensity of producing unexpected results by varying even one of a number of variables (i.e., temperature, concentration of substance, partial pressure, and the like) in a given supercritical system.

8. In my opinion, Hutchenson et al. accurately represents the state of the art at the effective priority date of the instant application (December 7, 2000). Additionally, I have searched for but have been unable to locate any other publications after Hutchenson and before December 7, 2000 directed to a description of the state of the art (such as a review paper) as presented in Hutchenson et al. As such, Hutchenson et al. accurately describes the unpredictability of supercritical fluid behavior and the difficulties of adequately and quantitatively predicting such behavior. Hutchenson et al. state that state-of-the-art equations-of-state (EOS) are still not capable of adequately and quantitatively predicting SCF behavior even in the simplest of

systems. Hutchenson et al. also state that the difficulties in correlating data are even more pronounced when the systems are more complex, such as when the chemical characterization of the solutes is not straight-forward (such as proteins), when high purity material is not readily
available and when the solubility of the solute in the supercritical CO_2 is low. Hutchenson et al. further state that "the impact that such uncertainties would have on the scale-up process should they not be recognized could well be economically and technically catastrophic."

9. In my opinion, the process of the present invention differs from the process described in Debendetti et al. in that the process described in Debendetti et al. does not provide an aqueous, non-gaseous fluid containing the substance and does not provide a dense gas including an anti-solvent and a modifying agent.

10. In my opinion, even with the benefit of hindsight at least two substantial changes would need to be made to the most relevant examples of the process disclosed in Debendetti et al. to arrive at the present invention, namely, to use an aqueous, non-gaseous fluid and to include a modifying agent with the anti-solvent.

11. In my opinion, the effect of one change on the outcome of the process would be difficult for one of ordinary skill in the art to predict, and simultaneously introducing a second change in the process would mean that the prediction of the outcome of the process would be almost impossible. This is mainly because even if it were possible to reliably predict the effect of the modification of one variable on another, one cannot predict the effect of that modification on all the other variables because it is unpredictable how the modification will affect the overall system. Predicting the behaviour of a compound in a dense gas process is by no means a matter of routine for the skilled researcher in the art and requires significant intellectual effort. This is mainly due to the complexity and unpredictable nature of supercritical systems that results from

the high propensity of producing unexpected results by varying even one of a number of variables (i.e., temperature, concentration of substance, partial pressure, and the like) in a given supercritical system. Therefore, even if one were to modify the process by including only one change to the process, such as including a modifying agent with the anti-solvent, one cannot predict the effect of that modification on all the other variables because it is unpredictable how the modification will affect the overall system.

12. The unpredictable nature of supercritical systems is evident in the Examples of the instant patent application. The Examples describe the method of the present claims including dissolving a substance in an aqueous non-gaseous fluid (i.e. water) that is substantially free of an organic fluid and supplying a modifying agent with the anti-solvent.

13. The process employed in the Examples of the present application produce unexpected results over the teachings of Debendetti et al. For instance, Example 2 of the present application teaches production of insulin solutions having a concentration of 100 mg/mL (see, paragraph [0089]) as compared to Example 2 of Debendetti et al. which teaches an insulin solution of 0.1 mg/mL (see column 9, lines 4 to 5). This higher concentration (by 3 orders of magnitude) in turn leads to higher throughputs and higher yields (see, for instance, Example 4 at paragraph [0095] where a yield of 90% is demonstrated). Such high concentrations and resulting yields are contrary to the teaching of Debendetti et al. in which water is to be avoided since it lowers the yield (see column 6, lines 28 to 32). Clearly, such a drastic increase in the yield demonstrated by the claimed method is superior and unexpected over the teachings of the prior art.

14. The undersigned further declares that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

30 JUN 2008
Date

Dr. Linda Sze Tu

Curriculum Vitae

Name: Linda Sze Tu

Education:
PhD (Chemical Engineering), University of New South Wales, 2000.
Bachelor of Engineering (Chemical Engineering), Honours Class 2 Division 1, University of New South Wales, 1996.

Research:
Head of Operations (2006-current), Eiffel Technologies Ltd.
Project Engineer (2003-2006), Eiffel Technologies Ltd.
Project Engineer (2000-2003), James Hardie Research
Postdoctorate Research (Mar-Jun 2000), Pharmaction Holdings Ltd.
Postdoctorate Research (Nov-Feb 2000), CRC Polymers
Postgraduate Research (1996-2000), University of New South Wales
Engineering Researcher (1995), University of New South Wales
Casual Researcher (Jan-Feb 1995), Gradipore Ltd.

List of Publications:
Sze Tu, L., Dehghani, F., Foster, N. R., Dillow, A. K., "Applications of Dense Gases in Pharmaceutical Processing", Proceedings of the 5th Meeting on Supercritical Fluids, Nice, France, March Volume 1, 263 (1998).

Thiering, R., Charoenchaitrakool, M., Sze Tu, L., Dehghani, F., Foster, N. R., Dillow, A. K., "Crystallisation of Para-hydroxybenzoic Acid by Solvent Expansion with Dense Carbon Dioxide", Proceedings of the 5th Meeting on Supercritical Fluids, Nice, France, March Volume 1, 291 (1998).

Sze Tu, L., Dehghani, F., Foster, N. R., "Micronisation and Microencapsulation of Pharmaceuticals Using a Carbon Dioxide Antisolvent" Powder Technology, 126, 134-149 (2002).

Sze Tu, L., Dehghani, F., Foster, N. R., "Precipitation of High Molecular Weight Pharmaceuticals by the Aerosol Solvent Extraction System", Chemeca'99, Newcastle, Australia, 26-29 September (1999).

Thiering, R., Sze Tu, L., Dehghani, F., Foster, N. R., Bustami, R., Chan, H., "Micronisation of Proteins Using Dense Gas Techniques", United Engineering Foundation Meeting, Davos, Switzerland, November (1999).

Foster, N.R., Bezanehtak, K., Charoenchaitrakool, K.M., Combes, G., Dehghani, F., Sze Tu, L., Thiering, R., Warwick, B., Bustami, R., Chan, H.-K., "Processing Pharmaceuticals Using Dense Gas Technology", Proc. 5th International Symposium on Supercritical Fluids, Atlanta, GA, April (2000).